(19) Europäisch s Patentamt
Eur p an Pat nt Office
Offic europé n des br vets

(11) Publication number : **0 542 422 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **92309172.2**

(22) Date of filing : **08.10.92**

(51) Int. Cl.[5] : **B01L 3/00,** B01L 7/00

(30) Priority : **12.11.91 US 790365**

(43) Date of publication of application :
19.05.93 Bulletin 93/20

(84) Designated Contracting States :
CH DE FR GB LI

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(54) Multi-well microtiter plate.

(57) A system and method for the high volume processing of a plurality of minute liquid specimens uses a multi-well microtiter tray (12) which has a base (14) with a flat underside and a plurality of wells (18) that are formed on the base. As intended for the present invention there are eight hundred and sixty four wells formed on the base (14). Also, included in the system is a structure which has a heat transfer plate (34) for supporting the microtiter tray (12), and for effecting heat transfer with the liquid specimens in the wells (18) of the tray (12). In one embodiment, the plate itself functions as a heat source. Alternatively, the plate functions as a heat sink and a heating element mounted on the structure is employed to heat the liquid specimens which are held in the wells of the tray. For this alternative embodiment, operation of the plate can be controlled in concert with the operation of the heating element. By controlling the operations of the plate and the heating element, the system of the present invention can cyclically vary the heating of the liquid specimens for procedures such as DNA amplification. The base of the tray, and the bottoms of the wells in the base of the tray, are light transparent to selectively allow simultaneous photometric or fluorometric measurements of all liquid specimens being held on the microtiter tray.

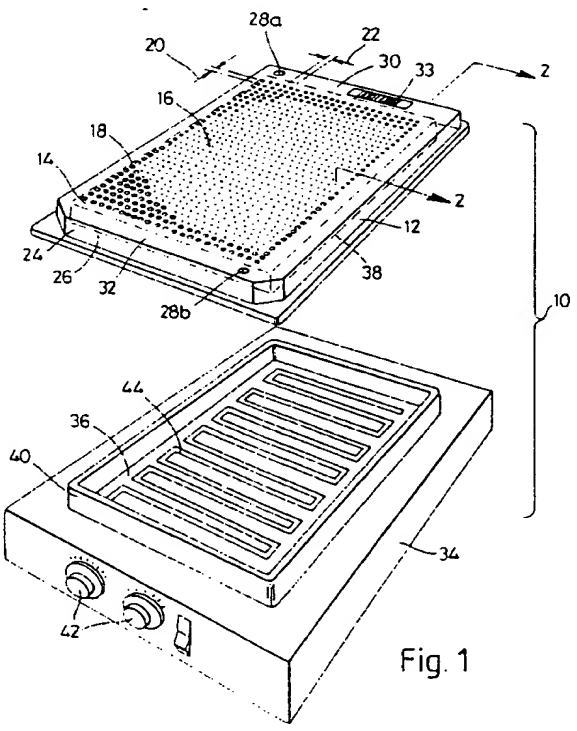

Fig. 1

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FIELD OF THE INVENTION

The present invention generally pertains to multi-well microtiter trays which are useful for holding a plurality of minute liquid samples. More particularly, the present invention pertains to microtiter trays which can hold a plurality of liquid specimens while they are being cultivated by a temperature varying regimen and during periodic photometric or fluorometric measurements of the specimens. The present invention is particularly, but not exclusively, useful for DNA amplification and sequencing.

BACKGROUND OF THE INVENTION

The laboratory processing of liquid samples has been accomplished in the past for many varied purposes. Examples of these purposes include cultivating cells in the specimens, transferring and storing the specimens, and using the liquid specimens for forensic purposes or to diagnose a diseased condition. Not unexpectedly, with advances in science the number and variety of such procedures is increasing and, in many instances, the procedures themselves are more complex and require increased precision. For one thing, this means that proper equipment must be used which is capable of performing the particular procedure with the required precision. Further, it means that the equipment must also be capable of efficaciously handling the liquid sample. And, in some cases, the ability of the equipment to handle the liquid sample may be no small matter. As is well known, many procedures require individual processing of a very large number of discrete liquid samples under the same or very similar conditions. Moreover, where expense is an overriding concern, additional factors need to be considered.

In instances where the cost of the sample material is significant, such as would clearly be the case for the processing of DNA specimens, there is a compelling interest to use as little of the material as is possible. For expensive sample material this interest is even more acute in instances where it.is necessary to process a very large number of discrete specimens of the sample material. Accordingly, there is a need for laboratory equipment which can efficaciously handle a relatively large volume of sample material as a large number of discrete and relatively minute specimens.

Microtiter trays with many wells for separately receiving liquid specimens have been used in the past to hold and store small specimens of sample material. Typically, these earlier trays have been designed for use with robotics which are capable of engaging the microtiter tray to deposit the specimens in the wells of the tray. In practice, the industry standard has been to provide microtiter trays which are separated by a center-to-center distance of nine millimeters. Accordingly, the robotics which are used with currently available microtiter trays have been designed to comply with this standard. This restriction on spacing between the wells. of the tray can be perceived as a disadvantage if the desire is to process as many discrete samples as possible. There are, however, other potential disadvantages in presently available microtiter trays.

In light of relatively recent advancements in specific areas of science, such as the processing of DNA samples, it is often desirable to have several functions accomplished while the liquid specimen remains in the well of the microtiter tray. For example, in the process of DNA amplification or sequencing, it is necessary for the liquid specimen to be subjected to a cyclical temperature regimen. Further, again for DNA amplification, it is desirable to periodically evaluate the specimen and determine whether the process is being accomplished successfully. It happens that this evaluation can be effectively done by taking photometric or fluorometric measurements of the liquid specimens. Thus, there is a need for a multifunctional microtiter tray. Specifically, in addition to providing increased storage capacity and enhanced ease in handling minute liquid specimens, it is desirable to have a microtiter tray which can be used in processes which vary and maintain the temperature of the specimens according to predetermined temperature regimens, and which can be used during photometric or fluorometric analysis of the specimens.

In light of the above it is an object of the present invention to provide a multi-well microtiter tray which is useful for simultaneously processing a high volume of minute liquid samples. Another object of the present invention is to provide a multi-well microtiter tray which is efficient in handling a very large number of individual minute liquid specimens. Yet another object of the present invention is to provide a multi-well microtiter tray which is useful with robotics which function in accordance with existing standards of the industry. Still another object of the present invention is to provide a multi-well microtiter tray which minimizes the storage space which is required for a very large number of minute liquid specimens. Another object of the present invention is to provide a multi-well microtiter tray which allows for substantially even heating of all liquid specimens being held in the tray. Yet another object of the present invention is to provide a multi-well microtiter tray which has sufficiently good optical qualities to allow for simultaneous photometric or fluorometric measurements of the liquid specimens in the tray. Yet another object of the present invention is to provide a multi-well microtiter tray which is simple to use, relatively easy to manufacture and comparatively cost effective.

SUMMARY OF THE INVENTION

A multi-well microtiter tray for use in a system, or

in a method, for high volume processing of a plurality of minute liquid specimens includes a generally rectangular base having a substantially flat underside. The top of the base is formed with a very large number of wells for holding a very large number of individual liquid specimens. As specifically intended for the present invention, the top of the microtiter tray is formed with eight hundred and sixty four wells which are arranged in a rectangular array that is thirty-six by twenty-four. Each well in the array has an opening and a bottom and is substantially cylindrical shaped to define a curved wall which tapers inwardly from the opening of the well to the bottom of the well. The bottom of each well is distanced from the underside of the base and has an optical quality surface for transmitting light through the underside and through the liquid specimens held in the well. The bottom of each well may be either flat, or rounded, or cone-shaped.

The system for using the multi-well microtiter tray includes a support structure which has a heat exchanger that is engageable with the microtiter tray. In one embodiment of the present invention, the heat exchanger is a heat source which conductively transfers heat to the liquid specimens in the well through th base of the microtiter tray. In another embodiment of the present invention, the heat exchanger acts as a heat sink and the support structure further includes a heating element. As one example, this heating element may be a heat radiator such as would be th case for a microwave oven. Preferably, however, the heating element comprises a plurality of heating probes which can be inserted into selected wells of the microtiter tray to conduct heat through the tray to the other wells in the microtiter tray. For the embodiments where the heat exchanger is to be used as a heat sink, the system can also include a controller to coordinate the operation of the heating element with the operation of the heat exchanger to cycle the liquid specimens through predetermined temperature regimens.

Due to the construction of the base of the microtiter tray, light can be transmitted through the liquid specimens for photometrically or fluorometrically measuring the characteristics of the liquid specimens. This can be simultaneously done for all of liquid specimens held by the microtiter tray as they are being processed. Processes which can be accomplished using the system and methods for using a microtiter tray as intended for the present invention include DNA amplification sequencing and library construction.

The novel features of this invention, as well as the invention itself, both as to its structure and its operation will be best understood from the accompanying drawings, taken in conjunction with the accompanying description, in which similar reference characters refer to similar parts, and in which:

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an exploded perspective view of the system of the present invention;

Figure 2A is a cross-sectional view of the preferred embodiment of the wells in the microtiter tray of the present invention as seen along the line 2-2 in Figure 1 shown schematically with a device for photometrically or fluorometrically measuring liquid specimens in the wells;

Figure 2B is a cross-sectional view of another embodiment of the wells in the microtiter tray of the present invention as would be seen along the line 2-2 in Figure 1;

Figure 2C is a cross-sectional view of yet another embodiment of the wells in the microtiter tray of the present invention as would be seen along the line 2-2 in Figure 1;

Figure 2D is an enlarged cross-sectional view of the preferred embodiment of the wells in the microtiter tray of the present invention as seen along the line 2-2 in Figure 1 showing dimensions for the wells and the engagement of a well in the microtiter tray with a probe;

Figure 3 is a perspective view of the system of the present invention in an operational environment with a robot;

Figure 4 is a perspective view of the system of the present invention operatively positioned for use with a microwave oven;

Figure 5 is a perspective view of the microtiter tray of the present invention engaged with a heat transfer tool;

Figure 6 is a cross-sectional view of the microtiter tray as seen along the line 6-6 in Figure 5;

Figure 7 is a perspective view of the system of the present invention in use with a probe heater; and

Figure 8 is a cross-sectional view of the microtiter tray engaged with a probe heater as seen along the line 8-8 in Figure 7.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring initially to Figure 1, the system for high volume processing a plurality of minute liquid specimens, is shown and generally designated 10. As shown, the system 10 includes a microtiter tray 12 which has a base 14. Formed into the top surface 16 of the base 14 are a plurality of wells 18. Specifically, as intended for the present invention, base 14 of microtiter tray 12 is formed with eight hundred and sixty four (864) wells 18 which are arranged in a rectangular array that is thirty-six by twenty-four (36X24). The center-to-center distances 20 and 22 between the rows and lines of the wells 18 are set at three millimeters (3mm). Additionally, it will be appreciated by reference to Figures 2A, 2B, 2C and 2D, in addition

to Figure 1, that base 14 is of a solid construction. Stated differently, there is no space between the wells 18. Instead, the material of base 14 fills what could otherwise be empty space between the wells 18. This construction helps provide temperature uniformity for all of the liquid specimens held in the wells 18 because base 14 establishes a shorter thermal path from a well 18 to another well 18 to facilitate heat transfer therebetween.

Preferably, microtiter tray 12 is made of an optically clear rigid plastic such as polystyrene, polypropelene, or polycarbonate. Additionally, the plastic of tray 12 can include carbon fibers, alumina, aluminum oxide, or other metals which will enhance the thermal conductivity of the tray 12 but which will not interfere with its biological performance. As intended for the present invention, the tray 12 can be manufactured by any process well known in the pertinent art, such as by injection molding.

Figure 1 also shows that microtiter tray 12 has an overhang 24 which forms a detent 26 between the overhang 24 and the base 14 of tray 12. Additionally, a pair of registration points 28a and 28b can be formed into top surface 16 of tray 12 in order to align the tray 12 with a robot (not shown in Figure 1) for purposes to be discussed below. Also, the top surface 16 of microtiter tray 12 has a flat area 30 and a flat area 32 on which an identification strip, such as bar code 33, can be placed. As will be appreciated by the skilled artisan, some ability to identify the microtiter tray 12 and the liquid specimens held in the wells 18 of the tray 12 can be essential.

As shown in Figure 1, the system 10 of the present invention includes a support structure on which microtiter tray 12 can be placed. At this point it is to be noted that, within the contemplation of the present invention, the support structure may be merely a storag shelf. For example the support structure may be part of a library for biological specimens", such as a shelf in a standard refrigerator (not shown) or an incubator (not shown). Regardless, in addition to the specific support structures disclosed below, it is intended that the support structure may encompass any platform where the microtiter tray 12, and the liquid specimens in the wells 18 of tray 12, can be stored for prolonged periods of time. In addition to the storage function of any particular support structure, a more operational function is for heat transfer with the liquid specimens. Specifically, when processing liquid specimens in the wells 18 of microtiter tray 12, the support structure is as a heat exchanger 34.

For the purposes of the present invention, heat exchanger 34 can be either a heat source or a heat sink. In either case, it must be operatively engageable with the microtiter tray 12. For the embodiment of heat exchanger 34 shown in Figure 1, heat exchanger 34 can have a surface 36 which will directly abut against the flat underside 38 of base 14 of the microtiter tray 12. Though not shown, it will be appreciated by the skilled artisan that a thermal grease, or some other such substance well known in the pertinent art can be placed on the surface 36 to facilitate heat transfer between the heat exchanger 34 and the microtiter tray 12. An additional feature of the system 10 of the present invention which promotes good heat transfer characteristics for the microtiter tray 12 is that both the top surface 16 and underside 38 of the tray 12 are flat and each have a relatively large area. Additionally, heat exchanger 34 can be formed with a ridge 40 which is matingly received into the detent 26 of microtiter tray 12 to help hold the tray 12 in position on heat exchanger 34. For the embodiment of the system 10 wherein the heat exchanger 34 acts as a heat source, the exchanger 34 can include controls 42a,b for the purpose of precisely controlling the amount of heat which is to be applied from the heating coils 44 of heat exchanger 34 to the tray 12 during the processing of the liquid specimens in the wells 18.

Actual configurations for the wells 18 will be best appreciated with reference to the Figures 2A, 2B, 2C and 2D. There, and with cross reference to Figure 1, it will be appreciated that each of the wells 18 in microtiter tray 12 is essentially a hollow cylindrical recess which is formed into the top surface 16 of the tray 12. Specifically, each well 18 has an opening 46 and is defined by a cylindrical sidewall 48 which extends from the opening 46 to the bottom of the well. In Figure 2A, a well 18 is shown to have a substantially flat bottom 50, whereas in Figure 2B the well 18 has a rounded bottom 52, and in Figure 2C the well 18 is shown with a cone shaped bottom 54. According to the particular needs of the user, a particular shape for the bottom of well 18 may be preferable. For instance, the rounded bottom 52 of well 18 is better suited for use with liquid specimens which include cells which might tend to cling to the angled surfaces presented by a flat surface 50. Further, the cone-shaped surface 54 might be preferable for use with automatic pipetting.

Regardless of their particular configuration, the bottoms 50, 52, and 54 of wells 18, as well as underside 38 of base 14, must be optically clear. Stated differently, sufficient light with which to make photometric or fluorometric measurements of the liquid specimens 56 being held in the well 18 must be able to pass through underside 38, through the bottom 50, 52, 54 of well 18 and through the liquid specimen held in well 18. For the purposes of the present invention, optically clear means that the bottom 50, 52, or 54 has a smoothness such that deviations in their surface do not exceed more than one quarter wavelength of the light which is passed through tray 12 and the liquid specimen 56 to mak photometric or fluorometric measurements of the liquid specimen 56. As intended for the present invention, and due in part to the plastic materials used for the manufacturing of tray 12, the

light used for photometric or fluorometric measurements of the liquid sp cimen 56 will be primarily in the visual range. The preferred dimensions for a typical w ll 18 will be best appreciated with specific reference to Figure 2D.

As indicated above, center-to-center distance 20 between adjacent wells 18 along either a line or a row of wells 18 is approximately three millimeters (3mm). Thus, a standard tool having a nine millimeter (9mm) spacing between probes can be used with the 3mm spacing of tray 12 if it is repeatedly used three times. This can be carried further. For example, in one embodiment for tray 12 the center-to-center distance can be four and a half millimeters (4.5mm). The standard robot would then need to be used twice. It happens that several configurations of the tray 12 can be used with standard robotics just so long as the center-to-center spacing is equal to nine divided by n, where n is an integer. Obviously, the volume capacity of the wells 18 will be sacrificed as more wells 18 and incorporated into the tray 12.

For a typical well 18 shown in Figure 2D, the diameter 58 of the opening 46 is approximately two millimeters (2mm). Though depicted with some exaggeration, Figure 2D shows that the sidewalls 48 of well 18 are tapered inwardly from the opening 46 of well 18 to its bottom 50. Specifically, the angle of taper 60 is approximately one degree (1°). The depth 62 of well 18 is approximately seven millimeters (7mm) with the result that well 18 is dimensioned to hold a liquid specimen 56 having a volume of approximately twenty microliters (20 ul). In many instances, however, the actual volume of the liquid specimen 56 which is to be deposited into a well 18 may have a liquid volume that is more on the order of one or two microliters (1-2 ul).

As is well known, liquid specimens which have total volumes on the order of one or two microliters can be hard to handle. A specific problem confronted by the present invention involves the transfer of such a small liquid specimen 56 into a well 18 of the microtiter tray 12. This problem stems from the fact that surface tension of the liquid specimen 56 will, at this level, be sufficient to prevent the specimen from forming into a drop which will fall into the well 18. Consequently, to assist the transfer of the liquid specimen 56 into the well 18, the sidewalls 46 of the well 18 are tapered.

Referring specifically to the well 18' shown in Figure 2D, it is contemplated by the present invention that a liquid specimen 56 will be transferred from a source of the liquid (not shown) to the well 18' of microtiter tray 12 by a device such as the probe 66. As stated above, the size of the liquid specimen 56 may be so small that it cannot form into a drop which will fall into the well 18'. However, since the sidewalls 48', of well 18' are tap red, probe 66 can be made to contact the sidewall 48' when it is inserted into the well 18'. This contact, a mere kiss if you will, is sufficient to wet the sidewall 48' with the liquid specimen 56 and cause the liquid specimen 56 to flow into the bottom 50' of the well 18'.

Referring now to Figure 3, it will be seen that a robot 68 may be used to transfer liquid specimens 56 form a source of the specimens (not shown) to the microtiter tray 12. Specifically, the robot 68 is outfitted with an end effector 70 which has a plurality of probes 66 (e.g eight hundred and sixty four) for this purpose. Each of the probes 66 is designed, in a manner well known in the pertinent art, to carry a minute quantity of a liquid specimen 56 for deposit on the tray 12. Further, the robot 68 can include well known means (not shown) on end effector 70 which will register with the registration points 28a,b on microtiter tray to properly align the probes 66 on end effector 70 with the wells 18 on microtiter tray 12. Though not shown, it will be appreciated that robot 68 is operable to engage end effector 70 with the microtiter tray 12 to deposit liquid specimens 18 in the wells 18 of tray 12.

Once the liquid specimens 56 have been deposited into the wells 18 of microtiter tray 12, heat exchanger 34 can be operated to heat the specimens 56 as desired by the user. This, of course, is for the embodiment of the system 10 wherein the heat exchanger 34 acts as a heat source. According to the present invention, various temperature regimens may be followed by the heat exchanger 34 when heating the specimens 56. DNA amplification is but one example of such a regimen.

Returning for the moment to Figure 2A, it will be seen that microtiter tray 12 is intended to be used during photometric or fluorometric measurements of the liquid specimens 56 which are deposited into the wells 18 of the tray 12. In Figure 2A a light source 72 is schematically shown in a relationship with the tray 12 for making such photometric or fluorometric measurements. The light source 72 may be of any type well known in the pertinent art, but it is preferably of a type which will emit a light 74 in the visual range having identifiable wavelengths, for example λ_1. According to standard photometric or fluorometric analysis a resultant light 76 having a different wavelength, for example λ_2, will result due to the particular characteristics of the liquid specimen 56. This resultant light 76 will then be received at a light detector 78 and the wavelength difference between light 74 and resultant light 76 can be used to measure the characteristics of the liquid specimen 56. As contemplated for the present invention, a photometric or fluorometric analysis of the liquid specimens 56 in microtiter tray 12 can be made at any time.

As indicated above, th heat exchanger 34 can be used as a heat sink as well as a heat source. Accordingly, when heat exchanger 34 is to a heat sink, another source of heat is needed for procedures wherein the liquid specimens 56 are to be cycled through a temperature regim n. Figure 4 indicates

that heat exchanger 34 can be incorporated as part of an oven 80 and that the microtiter tray 12 can be positioned on the exchanger 34 in oven 80. The door 82 of oven 80 can then be shut (not shown) to enclose microtiter tray 12 with its liquid specimens 56 inside the oven 80. Both the heating function of the oven 80, and the cooling function of the heat sink exchanger 34, can then be controlled from the control panel 84 to cycle the liquid specimens 56 in tray 12 through any temperature regimen desired by the user. As intended for the present invention, oven 80 may be of any type well known in the pertinent art. For example, oven 80 may be a microwave oven or it may be an air thermal cycler.

For those cases in which the oven 80 is an air thermal cycler, the system 10 of the present invention may also include a heat transfer tool 86. As shown in Figures 5 and 6, the heat transfer tool 86 comprises a block member 88 on which are mounted a plurality of heat probes 90 that extend through the block member 88. As best seen in Figure 6, the heat probes 90 each have and extension 92 which extends upwardly from the block member 88 and an engager 94 which extends downwardly from the block member 88. It will also be noted in Figure 6 that the heat probes 90 are mounted on the block member 88 of heat transfer tool 86 so that when the tool 86 is engaged with a microtiter tray 12 an engager 94 is inserted into only every other one of the wells 18. It will be appreciated by the skilled artisan that the probes 90 may be spaced more than one well 18 apart from each other. This alternating engagement between the heat probes 90 of heat transfer tool 86 and the wells 80 of tray 12 is followed along both the lines and rows of the array of wells 18 in microtiter tray 12. Figure 6 also indicates that a thermal grease 96 can be placed on the engagers 94 to assist in the transfer of heat from each of the heat probes 90 to the liquid specimens 56 in adjacent wells 18.

Once alternate wells 18 in microtiter tray 12 have been filled with liquid specimens 56, and the heat transfer tool 86 is engaged with the microtiter tray 12 substantially as shown in Figures 5 and 6, the combination of tray 12 and tool 86 can be placed on heat exchanger 34 in oven 80. Though the actual placem nt of this combination is not shown in Figure 3, it will be easily appreciated that a heat transfer tool 86 could be engaged with the microtiter tray 12 shown in Figure 3. As stated above, the assumption here has been that oven 80 is a thermal air cycler. Accordingly, with the tool 86 and tray 12 combination in oven 80, hot air can be circulated across tool 86 to heat the extensions 92 of heat probes 90 on heat transfer tool 86. This heat from the extensions 92 will then be conducted through each of the probes 90 to their r spective ngager 94 where it will be further conducted through bas 14 of tray 12 to heat the liquid specimens 56 in the wells 18 of microtiter tray 12. With the combination of microtiter tray 12 and tool 86, it will be appreciated that the liquid specimens 56 can be alternately heated or cooled by the air which is blown across extensions 92 by the oven 80. Accordingly, by varying the air temperature in oven 80, the tool 86 will be able to both heat and cool the liquid specimens 56 in tray 12. Again, heat exchanger 34 can be operated as a heat sink in concert with the heating of liquid specimens 56 by the heat transfer tool 86 to cycle the specimens 56 through any temperature regimen desired by the operator.

Figures 7 and 8 show yet another embodiment for the system 10 of the present invention wherein heat exchanger 34 is used as a heat sink. For this embodiment, the heating element for transferring heat to the liquid specimens 56 in wells 18 of the microtiter tray 12 incorporates a robot 98 which operatively maneuvers an end effector 100. As perhaps best appreciated with reference to Figure 8, the end effector 100 includes a plurality of probes 102 which are each engageable with one of the wells 18 of microtiter tray 12 substantially as shown in Figure 8. Similar to the arrangement disclosed above for heat transfer tool 86, the probes 102 of end effector 100 are spaced to be engageable with alternate wells 18 of the tray 18. Also as with heat transfer tool 86, this alternating arrangement extends along both the lines and the rows of wells 18 in tray 12. Here again, the ability of the probes 102 to transfer heat from the probes 102 to the tray 12, and eventually to the liquid specimens 56 in the adjacent wells 18, will be enhanced by the use of a thermal grease 104 which can be placed on each of the probes 102.

Figure 7 shows that a control box 106 is connected with heat exchanger 34 through a line 108, and that the control box is connected with robot 96 through a line 110. In any manner well known in the pertinent art, the control box 106 can be used to establish the temperature of the heating probes 102. Likewise, the control box 106 can be used to control heat sink 34 for removing heat from the specimens 56 in tray 12. Consequently, as with the other embodiments of the system 10 of the present invention, the embodiment shown in Figures 7 and 8 can be used to cycle the temperature of the liquid specimens 56 in the wells 18 of microtiter tray 12 according to any predetermined temperature regimen desired by the operator.

Though not specifically stated for each embodiment of the present invention, it is to be understood that photometric or fluorometric measurements can be made as desired. Specifically, the general procedure discussed above with reference to Figure 2A can be accomplished whenever required by the particular process being followed.

While the particular system and method for using a multi-well microtiter tray for the high volume processing of a very large number of minute liquid speci-

mens as herein shown and disclosed in detail is fully capable of obtaining the obj cts and providing the advantages herein before stated, it is to be understood that it is merely illustrative of the presently preferred embodiments of the invention and that no limitations are intended to the details of the construction or design herein shown other than as defined in the appended claims.

Claims

1. A system for high volume processing a plurality of minute liquid specimens characterised in that it comprises:

   means for separately holding said plurality of minute liquid specimens, said holding means including a plurality of separate light transparent pathways, each said pathway being in light communication with one said specimen to permit simultaneous photometric or fluorometric analysis of said plurality of liquid specimens; and

   means engageable with said holding means for maintaining said plurality of liquid specimens in a temperature controlled environment to cultivate said specimens.

2. A system according to Claim 1 wherein said holding means is a microtiter tray having a base with a substantially flat underside, and having a plurality of wells formed on said base for individually receiving one said liquid specimen therein, each said well being oriented substantially perpendicular to said underside and having a bottom distanced from said underside, said tray further having a detent formed on said base around said underside.

3. A system according to Claim 1 or 2 wherein said engageable means is a support structure including a heat exchanger engageable with said detent for firmly holding said microtiter tray.

4. A system according to any one of Claims 1 to 3 wherein said temperature controlled plate is a heat sink, said support structure includes a heating element, and said system further comprises means for coordinating the operation of said heating element for heating said liquid specimens, with the operation of said heat sink to remove heat from said liquid specimens, for cyclically changing the temperature of said liquid specimen in each said w ll of said microtit r tray in accordanc with a predetermined regimen.

5. A system according to Claim 3 wherein said heat exchanger is a heat source for conductiv ly heating said liquid specimens held in said wells of said microtiter tray.

6. A system according to Claim 4 or 5 wherein said heating element is a source of microwave radiation.

7. A system according to Claim 4 wherein said heating element comprises a plurality of heating probes insertable into selected said well to heat said liquid specimens in other said wells.

8. A system according to Claim 7 wherein said support structure further comprises means for coordinating the conduction of heat energy from said heating probes to said liquid specimens with the activation of said heat sink to remove heat from said liquid specimens for cyclically changing the temperature of said liquid specimen in each said well of said microtiter tray in accordance with a predetermined regimen.

9. A multi-well microtiter tray for use in a system according to any one of Claims 1 to 8 characterised in that it comprises:

   a base having a substantially flat underside;

   a plurality of wells formed on said base for individually receiving one said liquid specimen therein, each said well being oriented substantially perpendicular to said underside, and each said well having a bottom distanced from said underside to establish a portion of said base between said underside and said bottom of each said well; and

   a detent formed on said base around said underside engageable with means on a support structure of said system.

10. A microtiter tray according to Claim 9 wherein each said well has an opening into said well and said well is substantially cylindrical in shape to define a wall, said wall of said well being tapered inwardly from said opening to said bottom of said well to facilitate receiving said liquid specimen in said well.

11. A microtiter tray according to Claim 9 or 10 wherein said bottom of each said well has a surface with sufficient optical quality to permit photometric or fluorometric measurement of characteristics of said liquid specimen in said well using light passing through said portion of said base.

12. A microtiter tray according to any one of Claims 9 to 11 wherein each said well is substantially cylindrical in shape and wherein said bottom of each said well is substantially flat.

13. A microtiter tray according to any one of Claims 9 to 11 wherein said bottom of each said well is rounded to establish a substantially hemispherical shape for said surface.

14. A microtiter tray according to any one of Claims 9 to 11 wherein said bottom of each said well is cone shaped.

15. A microtiter tray according to any one of Claims 9 to 14 wherein said base is made of a rigid clear plastic.

16. A microtiter tray according to any one of Claims 9 to 15 wherein each said well has a displaced volume of twenty microliters (20 ul).

17. A microtiter tray according to any one of Claims 9 to 16 wherein said plurality of wells comprises eight hundred and sixty four (864) wells.

18. A microtiter tray according to Claim 17 wherein said wells are arranged in a thirty-six by twenty-four array (36x24).

19. A microtiter tray according to any one of Claims 9 to 18 further comprising at least two indentations on said base for relative registration of said microtiter tray.

20. A microtiter tray according to any one of Claims 9 to 19 wherein said base further comprises means for identifying said liquid specimens in said microtiter tray.

21. A system according to any one of Claims 1 to 8 including a microtiter tray according to any one of Claims 9 to 20.

22. A method for high volume processing a plurality of minute liquid specimens which is characterised in that it comprises the steps of:

Placing a plurality of discrete minute liquid specimens in a microtiter tray having a base with a substantially flat underside, said tray also having a plurality of wells formed on said base for individually receiving one said liquid specimen therein, each said well being oriented substantially perpendicular to said underside and having a bottom distanced from said underside;

Mounting said microtiter tray on a support structure having a heat exchanger engageable with said microtiter tray, said heat exchanger being operable to change the temperature of said liquid specimen in each said well of said microtiter tray in accordanc with a predetermined regimen;

Establishing the temperature of said temperature controlled plate to cultivate said liquid specimens; and

Photometrically or fluorometrically measuring the characteristics of all said liquid specimens in said microtiter tray.

23. A method according to Claim 22 wherein said heat exchanger is a heat sink and said support structure further comprises a heating element and said method further comprises the steps of:

Transferring energy from said heating element to heat said liquid specimens in said wells of said microtiter tray;

Activating said plate to remove heat from said liquid specimens; and

Coordinating the radiation of energy from said heating element for heating said liquid specimens with the activation of said heat sink to remove heat from said liquid specimens for cyclically changing the temperature of said liquid specimen in each said well of said microtiter tray in accordance with a predetermined regimen.

24. A method according to Claim 23 wherein said transferring step is accomplished by heat radiation.

25. A method according to Claim 23 wherein said transferring step is accomplished by heat conduction.

26. A method according to any one of Claims 22 to 25 wherein said photometric or fluorometric measurements are accomplished by passing light through said underside of said base and simultaneously through said bottom of each said well.

27. A method according to Claim 23 wherein said predetermined regimen is DNA amplification, sequencing or library construction.

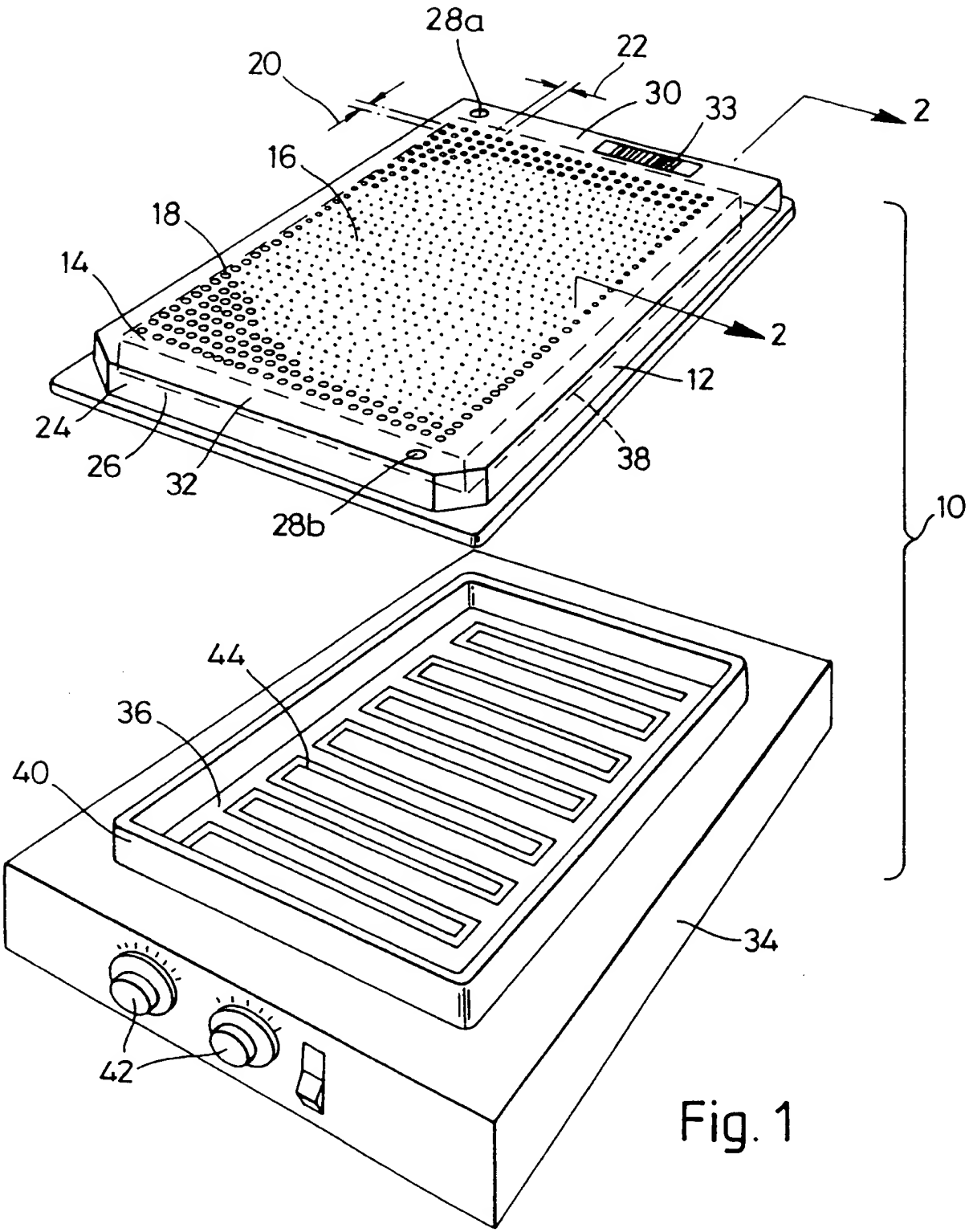

Fig. 1

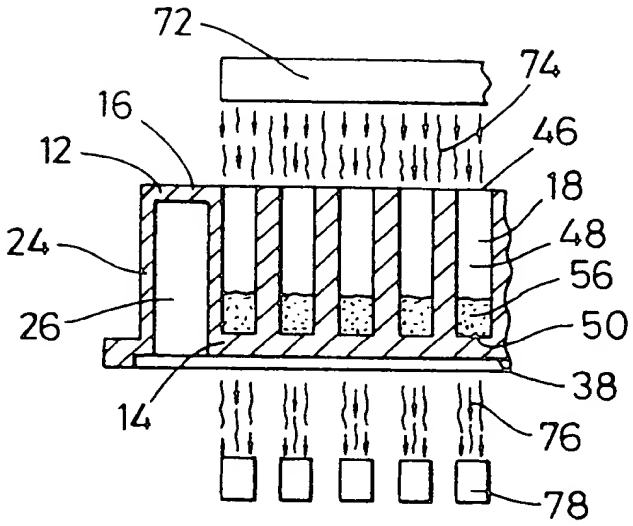

Fig. 2A

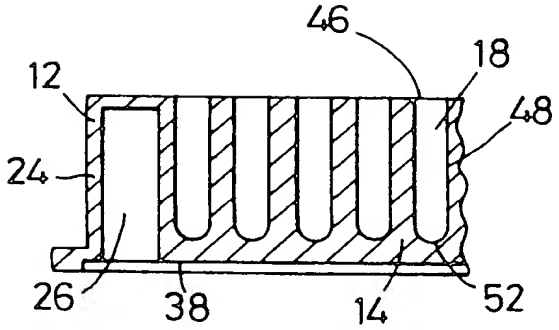

Fig. 2B

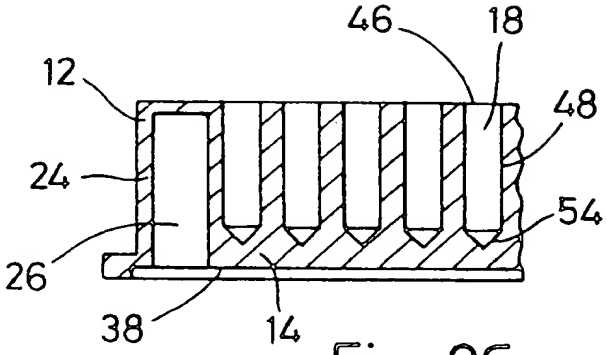

Fig. 2C

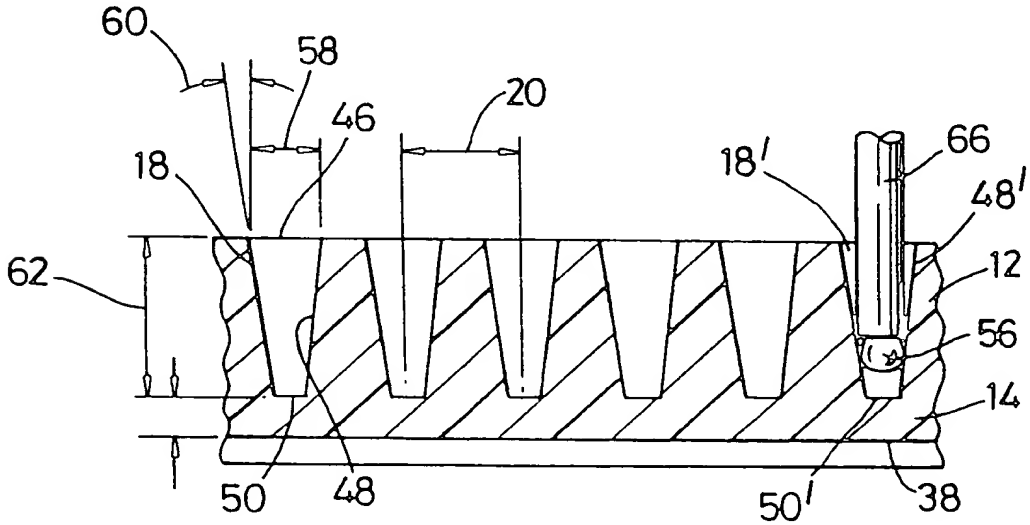

Fig. 2D

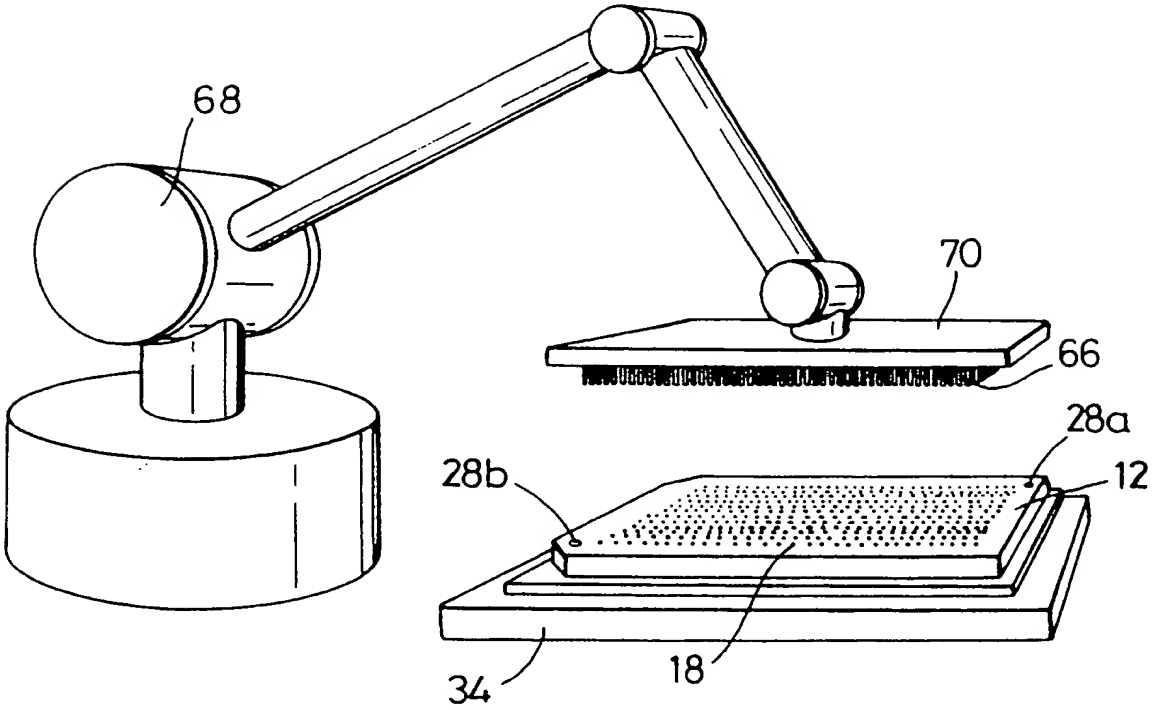

Fig. 3

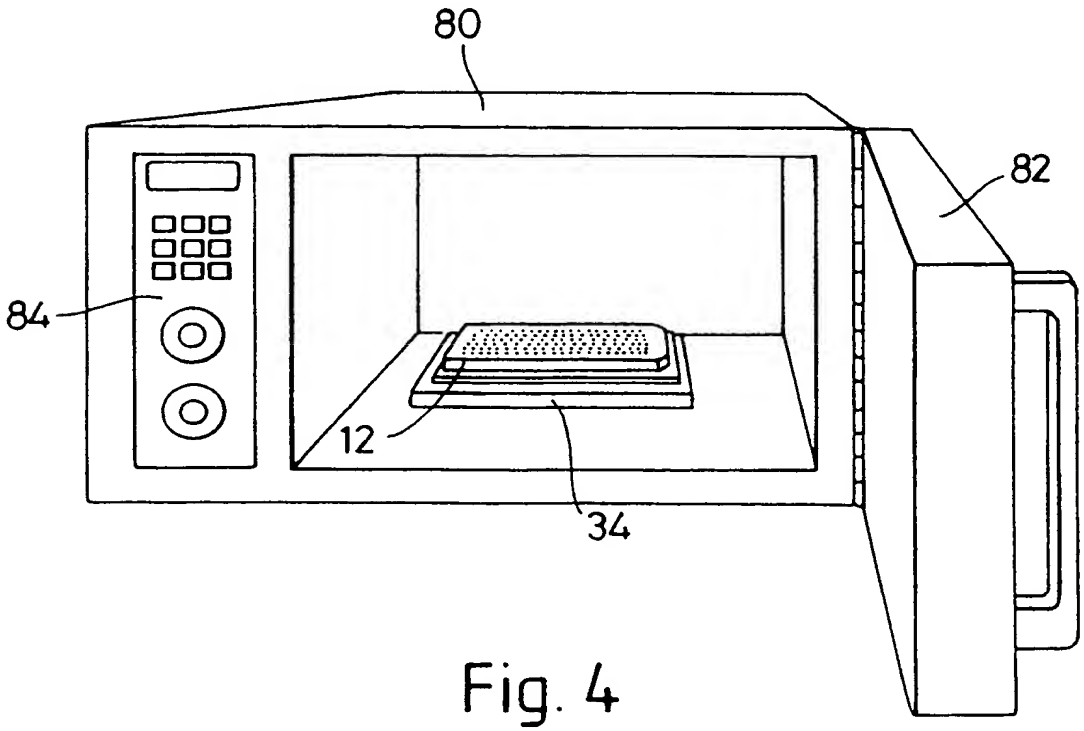

Fig. 4

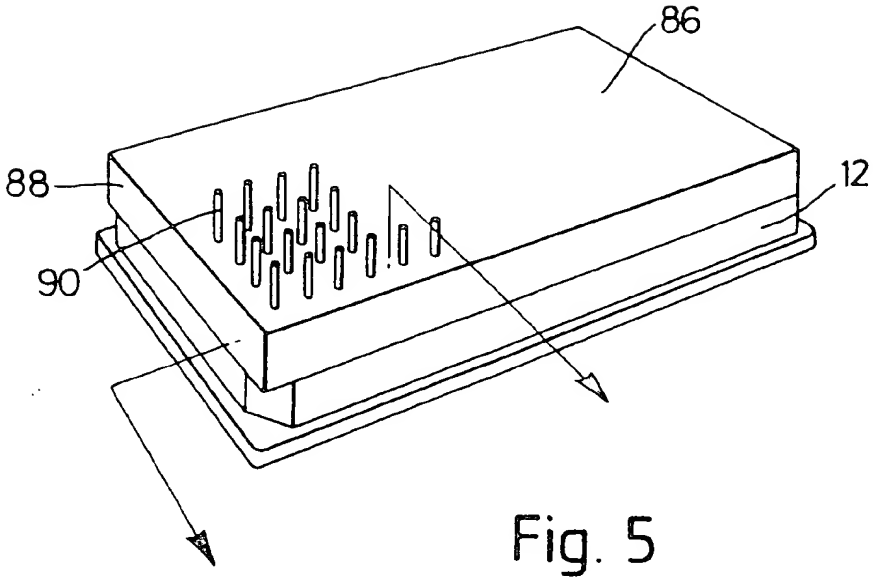

Fig. 5

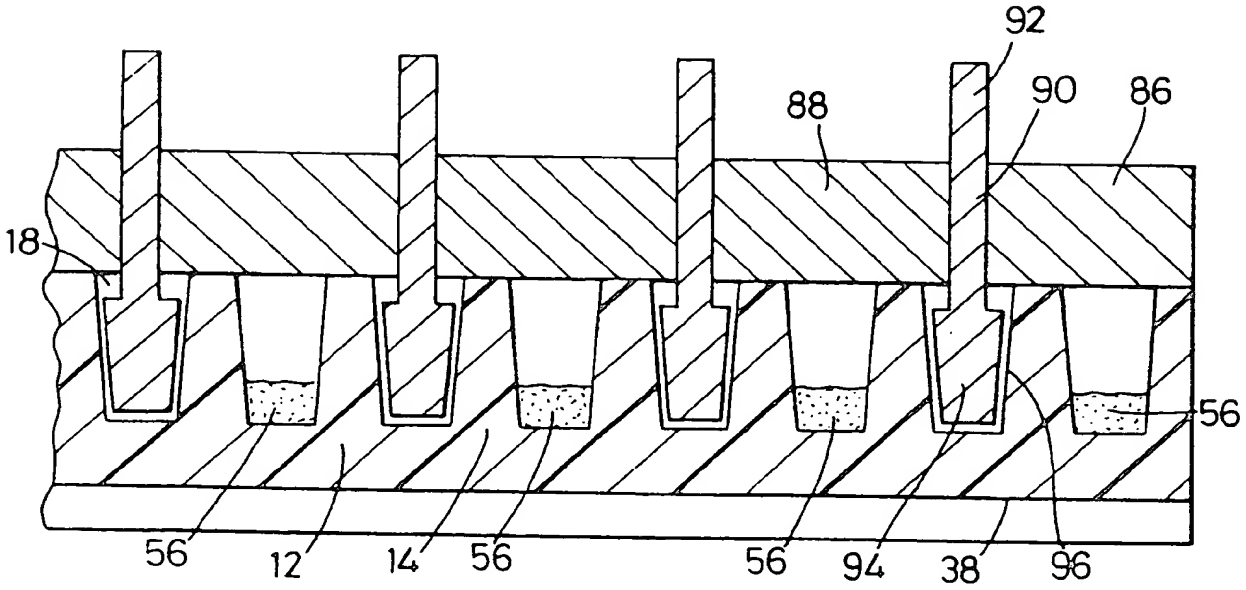

Fig. 6

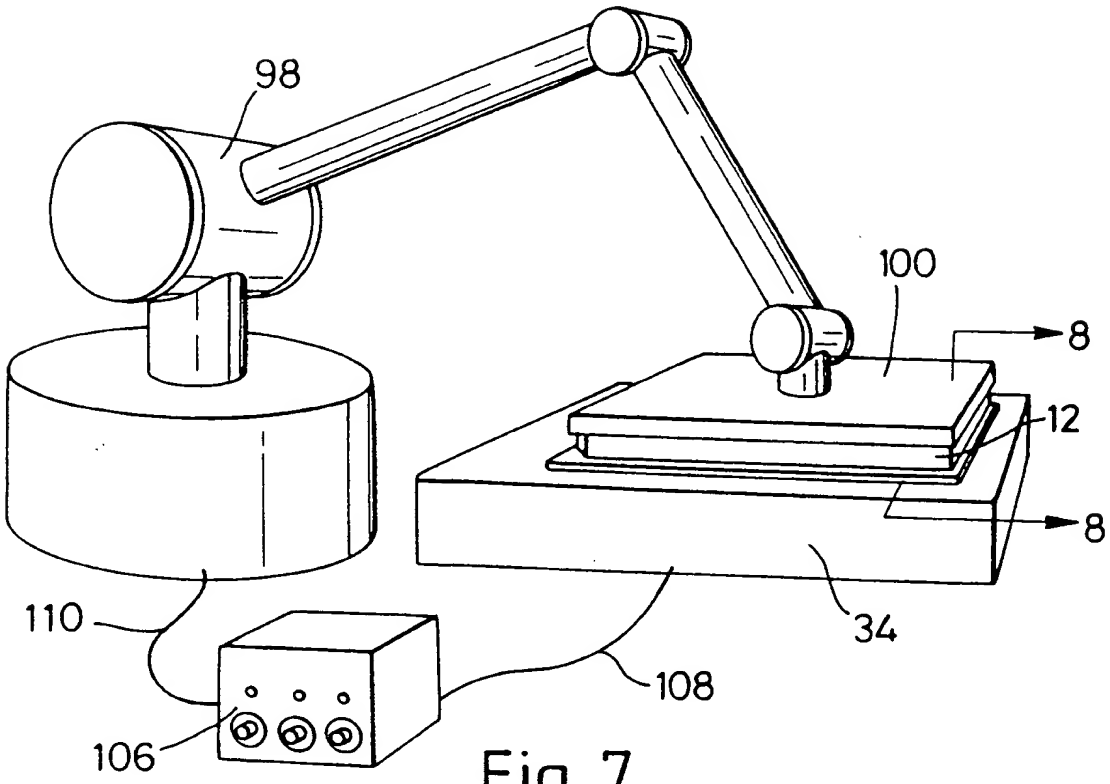

Fig. 7

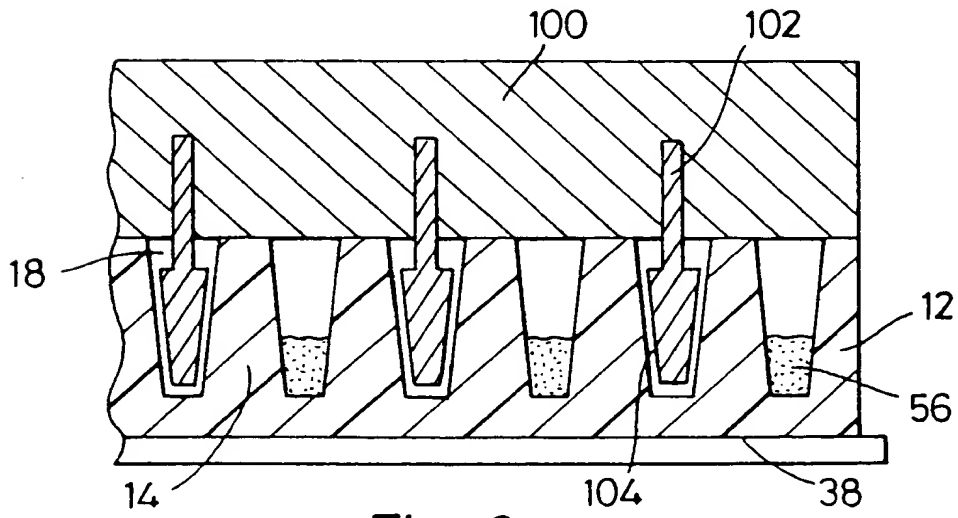

Fig. 8

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 9172

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X A	EP-A-0 408 280 (TECHNE) * the whole document *	1 2-5, 9-15, 21, 22, 25-27	B01L3/00 B01L7/00
X A	US-A-4 599 315 (TERASAKI ET AL.) * column 3, line 62 - column 6, line 45 *	1 2, 9-12, 15, 16, 21, 22	
X A	WO-A-8 909 437 (DEAN ET AL.) * page 5, line 1 - page 12, line 1 *	1 2, 9, 21, 24-27	
X A	FR-A-2 250 991 (SUOVANIEMI) * page 7, line 27 - page 10, line 17 *	1 3, 9, 11-14, 19-21	
A	WO-A-8 912 502 (LEP SCIENTIFIC LTD) * page 3, line 29 - column 7, line 10 *	1-5, 9, 21	
A	EP-A-0 438 883 (BECKMAN INSTRUMENTS) * column 2, line 51 - column 7, line 29 *	1, 3-5, 9 21-23, 25, 27	TECHNICAL FIELDS SEARCHED (Int. Cl.5) B01L
A	GB-A-1 528 424 (LABOR MÜSZERIPARI MÜVEK) * page 2, line 15 - line 54 *	1, 2, 4, 7 9, 10, 14, 19, 21, 22	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29 JANUARY 1993	BINDON C.A.

CATEGORY OF CITED DOCUMENTS

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L : document cited for other reasons

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